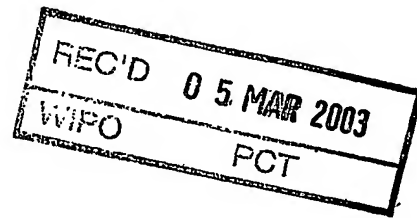


PCT/DK 03/00036  
10/501746

10 Rec'd PCT/PTG 16 JUL 2004



# Kongeriget Danmark

Patent application No.: PA 2002 00120

Date of filing: 23. January 2002

Applicant: Danfoss A/S

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## Patentansøgning

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Læs venligst vejledningen til de enkelte punkter

2. Ansøgers fuldmægtigs referencenr. 02 01 523 030

3. International indleveringsdag: ☐ Kapitel I  
Internationalt ansøgningsnr.: ☐ Kapitel II

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7. Opfindelsens benævnelse:

METHOD AND DEVICE FOR MONITORING ANALYTE CONCENTRATION  
BY USE OF DIFFERENTIAL OSMOTIC PRESSURE MEASUREMENT

8. Prioritetspåstand(e):

☐ Flere prioritetspåstande på bagsiden

Dato	Land	Nr.
Dato	Land	Nr.
Dato	Land	Nr.

9. ☐ Ansøgningen omfatter deponering af en prøve af biologisk materiale, som angivet i patentlovens § 8a, stk. 1.

10. ☐ Ansøgningen omfatter en sekvensliste.

11. ☐ Ansøgningen er fremkommet ved deling eller udskillelse.

Stamansøgningens nr.:

Ansøgt løbedag:

13. ☐ Ansøgningen er tidligere

indleveret pr. telefax den:

14. Dato og underskrift:

23. januar 2002

Danfoss A/S

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1.1-mard06

1. Gebyrer:

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☐ Kravgebyr

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12. Bilagsfortegnelse:

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Fig. nr. 2 \_\_\_\_\_ ønskes

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15. Behandling af fremmed-  
sproget ansøgning mm. ønskes

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5      Method and device for monitoring analyte concentration by  
         use of differential osmotic pressure measurement

10      This invention relates to biological sensors, more  
         specifically to implantable sensors for monitoring species  
         such as glucose, in a living creature. Further  
         specifically, this invention relates to biological sensors  
         for the detection of glucose in blood or tissue of a  
         diabetic patient.

15      Diabetic patients can improve their life quality  
         expectancy by maintaining their blood glucose  
         concentration close to the natural concentration of a  
         healthy person. To achieve this natural concentration,  
         diabetes patients must frequently measure their glucose  
20      concentration, and adjust their insulin dosing in  
         accordance with the measured concentration. Current  
         technology requires that a blood sample be obtained for  
         measurement of blood glucose concentration, and there are  
         a number of different glucose test kits on the market,  
25      based on measurement from a blood sample. The disadvantage  
         of these test kits is the blood sample, which must be  
         collected from a suitable place in the body.

30      Self monitoring devices, based on capillary blood glucose,  
         is practical, but still requires multiple frequent skin  
         punctures, which is inconvenient for the patient, and  
         requires certain sanitation.

35      Implantable devices known in the art include  
         electrochemical devices and optical devices based on the

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creation of an electrical or optical signal by the consumption of the compound analysed for. An example is US 6,011,984, which discloses methods utilising an amplification component. The sensitivity and the  
5 responsivity of such devices are influenced by the formation of a bio film, e.g. fibrous encapsulation, which reduces the transport rate of the compound to the sensor. Depending on the specific sensor other mechanisms, which deteriorate the sensor performance of implanted devices,  
10 are also present, e.g. membrane de-lamination and degradation, enzyme degradation and electrode passivation.

The object of this invention is to provide an alternative way to overcome the discomfort and inconvenience for  
15 diabetic patients, by providing a non-invasive measurement method for glucose concentration. It is a further object of this invention to provide a method for non-invasive measurement where the influence of bio fouling on the value of the measured signal will be decreased.

20 As would be obvious to those skilled in the art, the measuring principle disclosed with this invention is not limited to implanted devices in diabetic patients for measuring glucose concentration, but could be used in many  
25 other applications. The basic idea is used for measuring species in locations which are difficult to access, and where the physical- and chemical conditions vary over time. This could be measuring of glucose concentration in a bioreactor, measuring of glucose in fruit juice etc.

30 The object of this invention is achieved by utilising the osmotic pressure differences in compartments on the either side of a membrane, which is not permeable for the analyte in question. This principle is well known and is utilised  
35 in commercially available osmometers, such as supplied by

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e.g. Advanced Instruments, Inc. or Gonotec GmbH., in numerous clinical, research and industrial applications for measuring solute concentration.

- 5 The above products rely on an osmotic membrane separating a sample from a reference solution and measuring the osmotic pressure due to the difference in concentration between reference solution and sample.
- 10 The invention disclosed here differs from the above described by utilising two barriers or sets of barriers with different permeability characteristics, each membrane separating a compartment with a reference solution from the sample. The invention relies on the measurement of the
- 15 difference in osmotic pressure of the two compartments. The difference in osmotic pressure in the two compartments will reflect the concentration of species in the sample, which can permeate one of the two barriers, but not the other.
- 20 In one embodiment of the invention, the permeability of the two sets of barriers, separating the two compartments, are such that a specific species will be able to permeate into one of the compartment, but not into the other
- 25 compartment. This is done by that the first set of barriers is permeable for species up to and including the size of a specific molecule, and the second set of barriers is permeable for species below the size of same specific molecule.
- 30 In another embodiment of the invention, some of the compartments are filled with a known solution of species, unable to permeate through the barrier defining the compartment. Herby is achieved that the filled
- 35 compartments will work as reference compartments, whereby

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the determination of the concentration of a specific species can occur through comparison with the reference compartments.

5 In a specific embodiment of the invention the permeability of the two sets of barriers are such that glucose will be able to permeate into one of the compartments, but not into the other compartment. Herby a sensor specific for detecting the concentration of glucose in a sample is  
10 achieved.

In another embodiment of the invention, the pressure difference between the two compartments is detected, whereby a value corresponding to the concentration of  
15 species defusing into one of the compartments, but not into the other, is obtained.

In a more specific embodiment of the invention a separate pressure sensor detects the pressure exterior to the two  
20 compartments. The influence of pressure variations due to conditions external to the device can hereby be compensated.

In another specific embodiment of the invention, the  
25 pressure sensing is at least partly formed as a deflection measurement of a flexible compartment, which will increase or decrease in volume when the pressure in the compartment increases or decreases.

30 In the following the invention is described in details with references to the drawings showing:

- Fig. 1: a principal embodiment of the invention showing two compartments with two barriers separating them from a sample compartment.  
35

- 5 -

- Fig. 2: a principal embodiment of the invention showing a device with two compartments, defined to the exterior by barriers.
- 5 - Fig. 3: a principal embodiment of a device where a barrier separates the two compartments.
- Fig. 4: a principal embodiment of a device containing differential pressure sensing means.
- 10 - Fig. 5: a principal embodiment of a device, realised through a three-layer silicon micro technology structure.
- Fig. 6: a principal embodiment of a device, realised through a five-layer silicon micro technology structure.
- 15 - Fig. 7: a principal embodiment of an implanted device and an external powering and receiving device.
- Fig. 8: a principal embodiment of a device as a ring formed structure.
- 20 - Fig. 9: an exploded view of the principal device of fig. 8.
- Fig. 10: an exploded view of the principal device of fig. 8, where the barriers are supported by a mechanical structure.
- 25 - Fig. 11: A principal embodiment of a device where one of the compartments is divided into multiple reference compartments.

On figure 1 the basic function of the invention is shown. A compartment 11 and another compartment 12 have a sample  
30 volume 3 between them, in which a sample of mixed species is contained. Between sample volume 3 and compartment 11 is a membrane 14 with a low molecular weight cut off (MWCO), meaning that only species of a comparatively small  
35 size will be able to diffuse from sample volume 3 into compartment 11. A dotted line indicates this low permeable

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membrane 14, with small distance between the dots. Between sample volume 3 and compartment 12 is a membrane 15 with larger MWCO, indicated by a dotted line with larger distance between the dots as where the case with line  
5 indicating membrane 14.

Hence after a two-digit number indicates the compartment with a low permeable membrane, containing first the figure number and then the number 1. This annotation applies for  
10 the compartments 11 and 12, and for the membranes 14 and 15.

In a initial situation the two compartments 11 and 12 will be filled to the same level with pure water, and the  
15 sample volume with a sample containing a specific compound (among others), which concentration is to be determined. In the present case, we will assume that it is the concentration of glucose in water that is to be detected. The membrane 14 will then not be permeable for glucose,  
20 and the membrane 15 will be permeable for glucose. As water containing glucose is supplied to the sample volume, glucose will permeate into the compartment 12 until the concentration in compartment 12 and the sample volume are equal. A similar permeation is unable to take place  
25 between the sample volume and the compartment 11, due to the MWCO of the membrane 14. As equilibrium always is sought, water will diffuse from compartment 11 to sample volume 3, in order to reduce the concentration of glucose in the sample. This water will pass on to compartment 12,  
30 as equilibrium between sample volume and compartment 12 is obtained. Consequently the concentration of water will drop in compartment 11 and rise in compartment 12, having a hydro static pressure difference as result. We now have a hydrostatic force, working from compartment 12 towards  
35 compartment 11, and we have a concentration equilibrium



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force working from compartment 11 towards compartment 12. As the Osmotic pressure between the two compartments is reached, the two forces will be in equilibrium, and the hydro static pressure difference between the two  
5 compartments will depend on the concentration of glucose in the water in the sample volume.

The membranes used with this invention can be based on a difference in molecular weight cut off (MWCO) between the  
10 two membranes. By choosing one membrane with a MWCO just below that of a specific molecule, and another membrane with a MWCO just above that, the difference, and the changes in difference, in osmotic pressure in the two compartments, will depend on the concentration of the  
15 specific molecule in the sample.

Referring now to figure 2, the two compartments 21 and 22 are placed with a diffusion proof separator 8 between them. The membranes 24 and 25 are then formed as the  
20 surfaces defining the compartments to the exterior. When a device as that principally shown in figure 2 is placed in a sample of different species, the basic function as described above will take place, and the pressure in the two compartments will fit an equilibrium situation. The  
25 two pressures are detected by pressure sensors 9a and 9b, whereby the pressure difference is obtained.

In figure 3 is shown a device where two compartments 31 and 32 are stacked on a base plate 10. Depending of the  
30 MWCO of membrane 35, species will diffuse into compartment 32, and depending on the MWCO of membrane 34 further on into compartment 31. The Osmotic pressure will then appear over the membrane 34, between the two compartments. The pressure is detected by two independent pressure sensors  
35 9a and 9b. The pressure sensor 9c is for the purpose of

- 8 -

detecting the surrounding pressure, whereby pressure variations can be eliminated.

In figure 4 is shown a device much similar to that of figure 3, but with a differential pressure sensor 9d instead of two independent pressure sensors.

In figure 11 is shown a device like that of figure 3 and 4, but in a 3D-view. A top compartment 112 is defined to the exterior by a membrane 115, and is defined to a bottom compartment by a membrane 114. The bottom part itself is divided into a number of compartments, here three, each containing a different and known concentration of a given compound. As there are different concentrations in each compartment, 111a, 111b and 111c, the differential pressure between compartment 112 and each of 111 will vary from each other. By determine which of the compartments 111 has a pressure below that of compartment 112, and which has a pressure higher, the compartment 111 with a pressure equal, or close, to that of compartment 112 can be determined, and hence the concentration of the given compound in compartment 112. The pressure sensor can hereby be substituted with a simple qualitative pressure detector, only capable of detecting the direction of a pressure difference.

Micro machining techniques can be employed for the realisation of the device. In figure 6 silicon micro-machined pressure sensors 9a and 9b are integrated with each of the two compartments 61 and 62. In this way, the device can be made very small, e.g. a few mm<sup>3</sup>, and thus easily be implanted in a suitable place in the human body. An implantable glucose sensor is hereby a possibility, if the surfaces defining the device are made of a biocompatible material. The two membranes 64 and 65 most

- 9 -

also be of a biocompatible material, or covered with a biocompatible layer, which do not influence the MWCO of the membrane.

5 Whereas figure 6 is a five-layer structure, comprising two membranes and three layers of materials, e.g. silicon, figure 5 shows a three-layer structure. In figure 5 the membranes are made of two different parts in the same layer, ordered side by side.

10

As the device can be used as an implantable device, the device may then be powered and data collected from an external device. For this purpose established techniques for biomedical telemetry can be used, e.g. inductively  
15 coupled load shift keying or LC resonance frequency modulation. Figure 7 shows the device of figure 6, placed underneath the skin 1, so that the tissues and body fluids containing the compound to be measured are in contact with the membrane or membranes of the implanted device. An  
20 external power supply and receiver 2, containing a transceiver system, e.g. the primary of a transformer 4, and electronics for signal and data analysis, logging and display 5, is placed external to the skin above the implanted device. A signal for the osmotic pressure will  
25 be transferred from the implanted device to the transceiver 4, and be data analysed and displayed in the electronic 5.

The signal can also be transferred optically using  
30 infrared light, e.g. by modulation of a infrared LED or laser diode, or by imaging the inflation/deflation of flexible compartments of the implanted device according to the difference in pressure of the compartments and the external tissue and fluids.

35

- 10 -

As the osmotic pressure is temperature dependent, and also the MWCO of membranes can be temperature dependent, the temperature, at which a level of concentration in a sample is determined, must be known. This is often the case, within relatively narrow borders, when we speak about implanted devices in human body. However the temperature sensitivity may be used to extend the dynamic range of a sensor, simply by perform a determination of the concentration at different temperatures.

10

In fig. 8 is shown a cooling / heating device, like a Pelletier element, formed as two rings around the two compartments. This is more easily seen in figure 9, showing an exploded view of figure 8. In figure 9 is shown a membrane 95 with large MWCO, a ring formed Pelletier element where the centre of the element forms the compartment 92, a membrane 94 with a low MWCO and a ring formed Pelletier element where the centre of the element forms the compartment 91. On top of the structure is placed a membrane 94, defining compartment 91 to the external area. With this element is it possible to perform measurements at different temperatures, hereby facilitating and improving the analysis.

25 In figure 10 is shown a device similar to that of figure 9, only with a rigid element 101 on either side of a membrane. The element 101 must have now influence on the MWCO of the membrane. The purpose of this rigid element is to prevent deflection of the membrane, due to the pressure difference across it. As there are no deflections of the membranes, the volume of the compartments will be nondependent of the relatively small pressure differences, and pressure sensors can be used as previous described. If however deflection of the membranes is possible, the volume of the compartments will vary with the pressure

- 11 -

difference, until no pressure difference exists. In this case the pressure sensors must be substituted with a deflection sensor, where the deflection of the membrane then correspond to the concentration of a given compound.

5

The detected signal on the device must be calibrated to a known concentration of species, either one time for all or preferably from time to time. Measuring the concentration in a sample, taken at the same time as the osmotic pressure measurement, could achieve this.

10

The formation of a bio film on the implanted device will have less effect than is the case for electrochemical devices or other devices, where the compound to be measured is consumed in the measurement process. The bio film may influence the response time with respect to changes in the concentration in the surrounding tissue and liquid, but it will still have little effect on the measurement itself.

20

The two compartments and membranes could be increased to three or more different compartments and membranes. By increasing from two to three or more compartments and membranes, the dynamic range of the sensor could be increased. Also more information is made available for data analysis to establish compound concentrations. More compartments and membranes also facilitate consistency and quality control of data.

30

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Claims

- 5 1. Device containing at least two compartments, each of  
them at least partially defined to the exterior by two  
sets of permeable barriers, the first set of barriers  
to one of the compartments being permeable for a set  
10 of species and the second set of barriers to the other  
compartment being permeable only for a subset of said  
species, whereby only an subset of species that  
permeate into said one compartment will permeate into  
said other compartment.
- 15 2. Device containing at least two compartments, one of  
them at least partially defined to the exterior by a  
first set of barriers permeable for a set of species,  
the other compartment separated from said one  
compartment by a second set of barriers permeable only  
20 for a subset of said species, whereby only an subset  
of species that permeate into said one compartment  
will permeate further on into said other compartment.
- 25 3. Device in accordance with claim 1 or 2, characterized  
in that said first set of barriers is permeable for  
species up to and including the size of a specific  
molecule, and said second set of barriers is permeable  
for species below the size of said specific molecule.
- 30 4. Device in accordance with claim 1 or 2, characterized  
in that at least one of the compartments is filled  
with a known solution of solvent and solutes, all  
solutes in said solution being unable to permeate  
through the barriers defining said compartment.
- 35

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5. Device in accordance with claim 3, characterized in that the specific molecule is glucose.
6. Device in accordance with claim 4, characterized in that one of the solutes in said solution is glucose.
7. Device in accordance with claim 1 or 2, characterized in that the device is implantable and has an outer surface of biocompatible material.
8. Device in accordance with claim 1 or 2, characterized in that the device further contains pressure-sensing means capable of sensing the pressure difference between said compartments.
9. Device in accordance with claim 8, characterized in that the pressure sensing means comprises a pressure sensor for sensing the pressure exterior to said compartments.
10. Device in accordance with claim 8, characterized in that the pressure sensing means contains a differential pressure sensor.
11. Device in accordance with claim 8, characterized in that the pressure sensing means at least partly is formed as a deflection measurement of a flexible compartment, which will increase or decrease in volume when the pressure in the compartment increases or decreases.

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Abstract

5 A method is provided for the determination of the  
concentration of compounds in body tissue and fluids. The  
method utilises two compartments containing reference  
solutions, which are separated from the sample by two  
different semi-permeable membranes, whereby a difference  
10 in osmotic pressure occurs in the two compartments due to  
compounds, which can permeate one of the membranes, but  
not the other. The difference in osmotic pressure reflects  
the concentration of these compounds. The method is  
especially suited for analysis for the concentration of  
15 glucose in blood or tissue of diabetic patients, where a  
device is implanted underneath the skin of the patient and  
where the method is carried out by using the implanted  
device.

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FIG 1

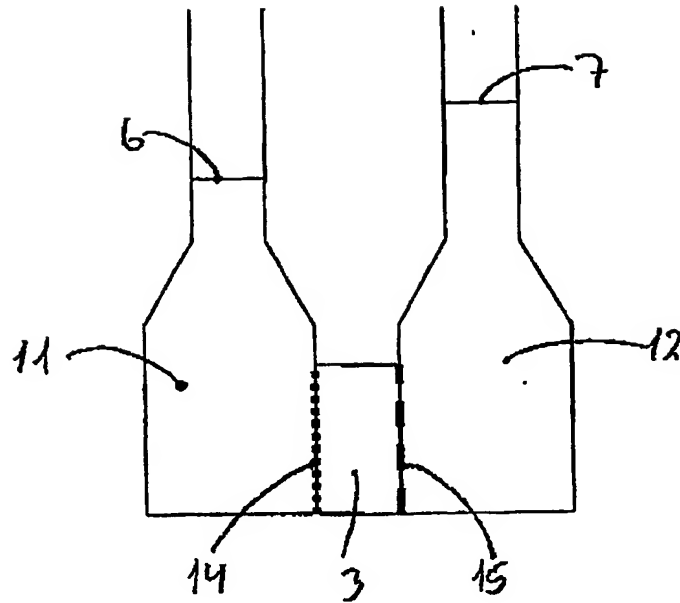
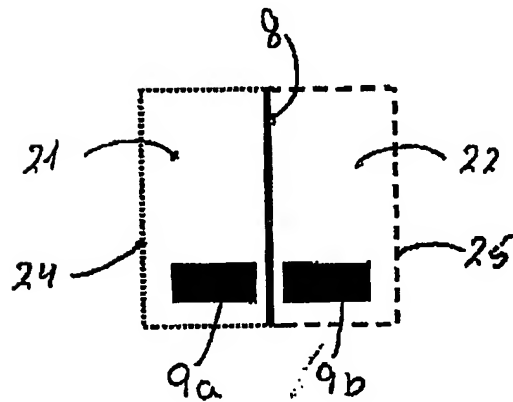


FIG 2



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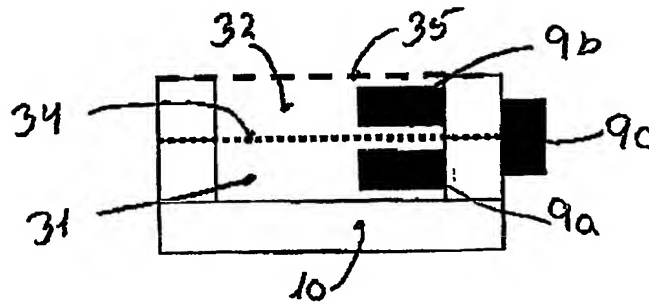


FIG 3

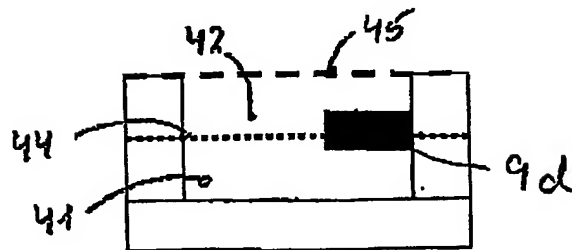


FIG 4

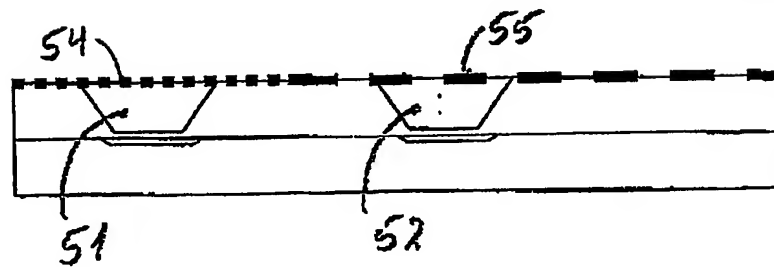


FIG 5

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FIG 6

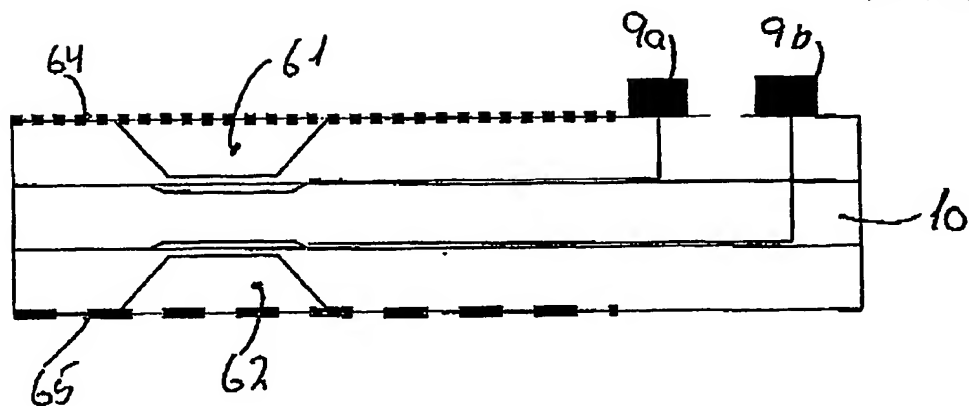
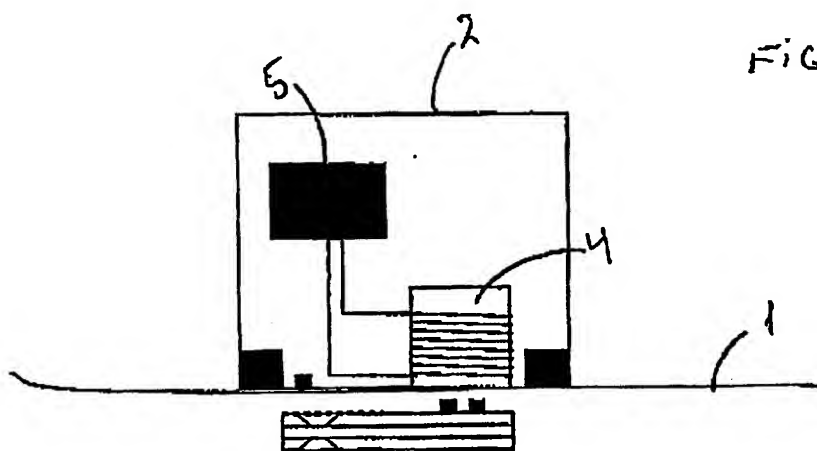


FIG 7



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Fig 8

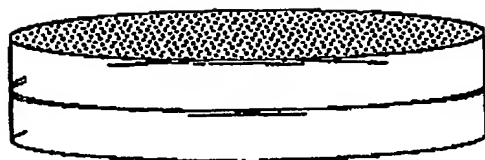


Fig 10

FIG 9

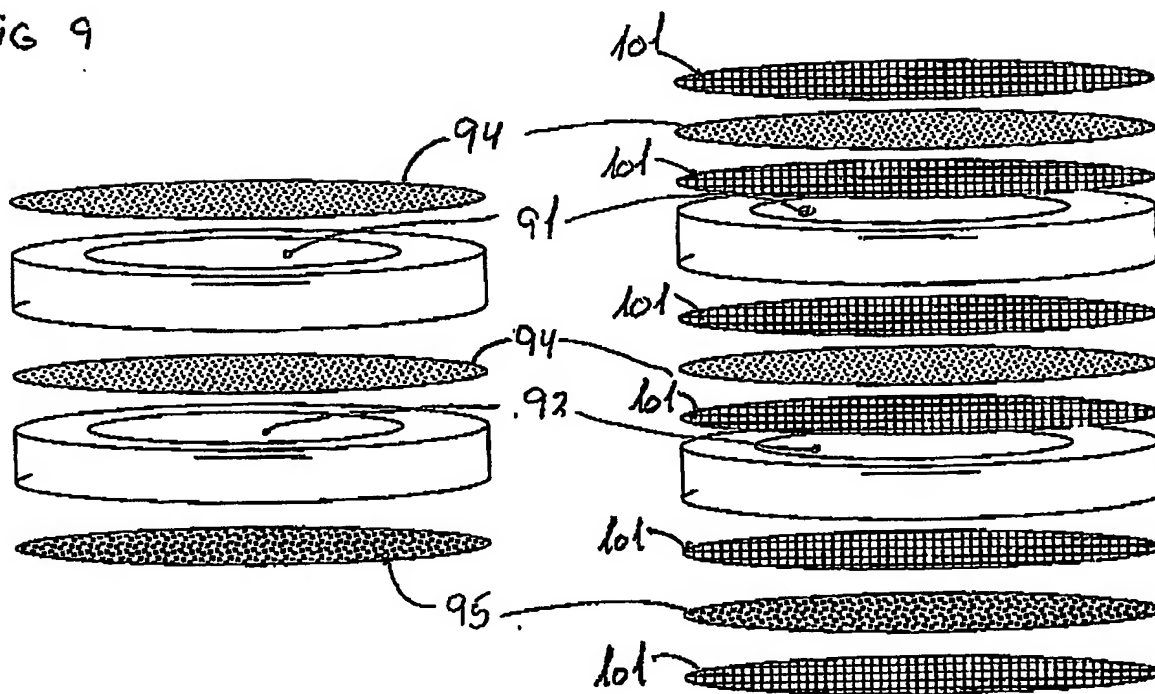
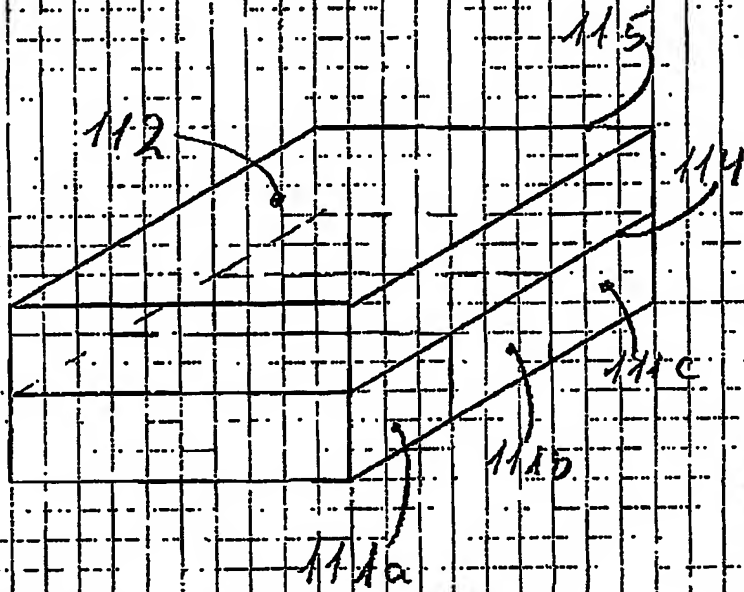


FIG 11



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